REMARKS

In the Action, claims 1, 3-8, 11 and 12 are rejected. In response, claims 1, 6, 7 and 11 are amended and claim 12 is added. In view of these amendments and the following comments, reconsideration and allowance are requested.

Rejections Under 35 U.S.C. § 112

On page 2, paragraph 5 of the Action, the rejection of clams 1 and 3-8 under 35 U.S.C. § 112, first paragraph, is maintained. In paragraph 15 on page 6, claims 11 and 12 are also rejected under 35 U.S.C. § 112, first paragraph. Claim 6 is rejected as being indefinite. The present amendment amends claim 6 to correct the clerical error noted in the Action. Claims 1, 7 and 11 are also amended to overcome the rejections.

The Examiner recognizes that the specification is enabling for Parkinson's disease and ischemia/reperfusion. Applicants respectfully submit that the specification is also enabling to one skilled in the art for the treatment of neurodegeneration diseases as claimed.

Claims 1 and 11 are amended to recite a method of "inhibiting" and for the "therapy" of neurodegenerative diseases and the symptoms of Parkinson's disease and ischemia reperfusion. As amended, the claims do not cover "preventing" or prophylaxis. Applicants submit that the claims as amended are enabled to one skilled in the art by the specification. As noted in the Action, the specification is enabling for treating Parkinson's disease and ischemia/reperfusion.

Attached is a Declaration by one of the inventors presenting test data to demonstrate the efficacy of the claimed compounds for the treatment of symptoms of Parkinson's disease, ischemia/reperfusion, Alzheimer's disease, stroke and brain ischemia, diabetes, balloon injury related neointima formation, cardiac ischemia reperfusion, myocardial ischemia, anti-hypertension activity, oral mucositis induced by acute radiation and sepsis induction. The

data presented in the Declaration as viewed by one skilled in the art established that the claimed compounds are effective and that he specification is enabling to one skilled in the art. Accordingly, Applicants submit that the specification is enabling for the claims as amended.

Rejections Under 35 U.S.C. § 103

Claims 1, 3-8, 11 and 12 are rejected under 35 U.S.C. § 103(a) over Paolini et al. in view of Ito et al., Floyd et al. and Atlas et al.

Applicants respectfully submit that it would not have been obvious to one skilled in the art to treat neurodegenerative diseases, Parkinson's disease and ischemia/reperfusion as recited in the claims based on the disclosures of Paolini et al., Ito et al., Floyd et al. and Atlas et al. either standing alone or in combination. The combination of the cited references do not suggest to one skilled in the method of inhibiting or therapy for neurodegenerative diseases with a reasonable expectation of success.

Paolini et al. only teaches to one skilled in the art that the compounds are able to capture oxygen free radicals associated with certain pathologies as disclosed in column 6, lines 35-41. Paolini et al. clearly provides no suggestion that the compounds are effective in treating or inhibiting the symptoms of neurodegenerative diseases. Furthermore, one skilled in the art would not be motivated to treat or inhibit the symptoms of neurodegenerative diseases and would have no reasonable expectation of success in treating neurodegenerative diseases based on the disclosure of Paolini et al. either alone or in combination with the secondary references.

Paolini et al. only discloses that the compounds can pass through lypophilic barriers. As noted in the previous response, the claimed compounds are able to pass through the blood-brain barrier to be effective in treating or inhibiting the symptoms of neurodegenerative diseases. The claims are amended to recite the method of administration of the claimed

compounds by oral, subcutaneous, intravenous, intramuscular or intrasternal administration. As amended, the compounds are not administered intrathecally or intracranially as suggested in the Action. Thus, the claims recite methods of administering the compounds such that the compounds pass through the blood-brain barrier.

As outlined in the attached Declaration, Paolini et al. does not suggest to one skilled in the art the claimed utility of the disclosed compounds. Paolini et al. refers only to treating symptoms of excess production of superoxide radicals. The treatment of excess superoxide radicals does not suggest to one skilled in the art that the compound would be expected to be effective for the treatment of neurodegenerative diseases.

Many authors including Ito et al. 1996, Floyd et al. 1992 and Atlas et al. found that oxygen scavengers are therapeutically effective in the treatment of oxidative stress dependent pathologies, (e.g., ischemia/reperfusion injury as disclosed in Floyd et al., and Parkinson's disease as disclosed in Atlas et al.) Although Paolini et al. discloses that the compounds are effective in getting into a cell to exert an antioxidant effect, this does not support the position that it would be obvious that the claimed compounds of formula (I) are effective in the treatment of the symptoms of ischemia/reperfusion injury and Parkinson's disease.

It is a universally accepted notion that each chemical compound, such as those with antiradical activity, is more or less effective on the basis of its peculiar chemico-physical properties and its action mechanism toward specific kinds of free radicals. Therefore, one skilled in the art cannot predict a possible benefit of an antioxidant in the one or another pathology where each disease possesses a specific or unique oxidative stress-related situation.

The ability of a compound to act as an oxygen scavenger does not provide an expectation of the therapeutic efficacy for treating the symptoms of a neurodegenerative disease. It has been found, for example, that the vitamin E supplemented diet is clearly effective in reducing hepatic and gastric lipid peroxidation (a typical outcome of oxidative

stress damage toward biological membranes) without any modification of stress-linked diseases such as gastric ulceration (Armario A. et al., 1990).

Moreover, the current evidence is sufficient to conclude that, in the human, the use of antioxidant vitamins such as Vitamin C and Vitamin E is able to reduce the oxidative stress (e.g. lipid peroxidation damage measured as F2-isoprostanes, the *in vivo* most predictive methodology available) (Mcall M.R and Frei B.,1999; Roberts L.J. and Morrow J.D. 2002). However, despite such evidence, clinical trials on antioxidant supplementation with these vitamins have failed to show any benefit with respect to the disease outcomes and sometimes have determined adverse effects (see, for example, Vivekananthan D.P. et al. 2003).

Paolini et al. teach that the compounds disclosed therein would be useful for the treatment of various diseases, including hyperbaric damage, suggesting that the compounds disclosed by Paolini et al. are capable of crossing the BBB to affect their antioxidant effect on the CNS. Paolini et al. teach that the compounds are lipophilic, and given the known lipophilicity, these compounds could cross the BBB, as disclosed in Wilkinson *(Goodman & Gilman's* The Pharmacological Basis of Therapeutics, 10th ed., 2001) which indicates that the more lipophilic a compound is, the more likely it will be capable of crossing the BBB.

On the other hand, Bloom *(Goodman & Gilman's* The Pharmacological Basis of Therapeutics, 10th ed., 2001) states that as cerebral ischemia modifies the BBB to increase access of substances (i.e. compounds of formula (I) to the CNS, crossing the BBB may not even be necessary. However, these statements and conclusions are deprived of a solid scientific basis and clearly at variance with the current International Literature (Medline, 2010).

Chemical antioxidants that are able to reduce hyperbaric oxygen-induced damage, such as beta-carotene, vitamin C, vitamin E and selenium (see, for example, Bitterman M. et al., 1994; Shang F., et al., 2002; Topal T. et al., 2004; Dundar K. et al., 2005) are unable to

reduce oxidative stress CNS-related pathologies such as Parkinson's disease, dementia, Alzheimer's disease, amyotrophic lateral sclerosis, motor neuron disease (see, for example, Fillembaum G.G. et al., 2005; Orrel RW. et al., 2008; Petersen RC. et al., 2005; Olanow C.W. 2003; Pappert E.J. et al., 1996).

With respect to the general assumption that the BBB is a dynamic barrier, where the permeability to drugs is expected to increase under certain conditions, Applicant submits that such conditions is a very limited phenomenon as clearly stated, for example, by Lichota J. et al., 2010. Neurodegenerative disorders are pharmacologically restricted to the use of small, mainly hydrophobic molecules, e.g. in chronic neurodegenerative diseases, like Parkinson's disease and in many psychiatric diseases, e.g. schizophrenia and major depression, where the vascular barriers are supposedly intact. The "targeting therapy strategy", a new approach for drug CNS-delivery which foresees the use of the conjugation between the targeting molecule and a specific drug carrier (cargo) is in contrast to the difficulty encountered in clinical setting linked to the failure of drugs in crossing BBB, have widely been proposed (Lichota J. et al., 2010). Furthermore, while inflammation can increase permeability, this fact is counterbalanced by other phenomena such as the stress which can markedly reduce the Pgp activity - a typical efflux pomp very active in the transport of substances across BBB (El Masry E. M. and Abou-Donia M. B., 2006). In addition, the increase permeability, when it occurs, is present only in a restricted CNS area but not in others, thus strongly limiting its presumed drug delivery-dependent advantage (Zhao C. et al., 2007; Carvey P. et al., 2009).

The CNS-oxidative stress related diseases modifies the BBB increasing access of substances to BBB itself, is automatically - from the therapeutically point of view - disavowed by the total absence of benefits derived by the use of the above mentioned traditional antioxidants. Notwithstanding that the diseases damage the BBB, the limited passage across the barrier is always the most evoked cause of the protection failure of the

molecule antioxidant, as clearly disclosed by Pappert et al. (1996). The Article abstract states "The lack of change may be due to limited passage across the BBB... negative studies on efficacy of alpha-tocopherol in Parkinson's disease need re-evaluation..." (Pappert et al., 1996). On the other hand, Wilkinson GR itself clearly affirms that the advantage related to the supposed increased permeability of the BBB by local damage to drugs is not supported by the scientific literature: "To date, however, such an approach has not been shown to be clinically useful" *(Goodman & Gilman's* The Pharmacological Basis of Therapeutics, 10th ed., 2001, page 10, col. 2, lines 44-48).

Paolini et al. provides no suggestion that the compounds of the present invention are able to pass through the blood-brain barrier. The passage in Paolini et al. referring to the double lypoproteinic layer does not refer to the blood-brain barrier and does not suggest to one skilled in the art that the compounds would be expected to pass through the blood-brain barrier.

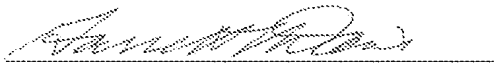
The secondary references do not provide a reasonable expectation to one skilled in the art that the compounds of Paolini et al. would be effective in treating the symptoms of neurodegenerative diseases or that he compounds could pass the blood-brain barrier. For example, Ito et al. provides no teaching that the compounds can be useful for the treatment of neurodegenerative diseases. The general disclosure in Ito et al. that oxygen free radicals cause various in vivo reactions do not provide a teaching that neurodegenerative diseases can be treated by the compounds of Paolini et al. The unpredictable nature of the treatment of neurodegenerative diseases and the unpredictable treatment of the symptoms would prevent one skilled in the art from having a reasonable expectation of success.

Floyd et al. and Atlas et al. do not overcome the unpredictable nature of the treatment of neurodegenerative diseases and treating the symptoms of neurodegenerative diseases. Clearly, all oxygen scavengers are not effective in treating neurodegenerative diseases or the

symptoms of neurodegenerative diseases. Therefore, one skilled in the art knowing the unpredictable nature, would have no reasonable expectation of the efficacy of the compounds of Paolini et al. for the treatment of neurodegenerative diseases. Accordingly, the claimed methods of inhibiting or the therapy of the symptoms of neurodegenerative diseases and Parkinson's disease and ischemia/reperfusion would not have been obvious to one skilled in the art based on the disclosures of the cited patents.

In view of the above comments, Applicants respectfully submit that it would not have been obvious to one skilled in the art that the claimed compounds would be effective in treating neurodegenerative diseases, Parkinson's disease or ischemia/reperfusion. Accordingly, reconsideration and allowance are requested.

Respectfully submitted,



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